

Board of Scientific Counselors

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ToxWorks

Styrene Draft Substance Profile

- A Classification Decision in Search of Justification

Proposed Classification

- Reasonably Anticipated to be a Human Carcinogen because of
 - A. limited evidence in humans
 - B. sufficient evidence in animals
 - C. supporting mechanistic data

Limited Human Data

- NTP Criteria - “a causal interpretation is credible”
- There is No evidence that a causal interpretation is credible

Kogevinas et al., 1994

- 6 significant differences out of 74 analyses; 4 were decreases.
- Profile asserts average exposure is better measure than cumulative.
- Average exposure derived mathematically from cumulative
- Genotoxic MOA argues for cumulative (linear response). Average exposure argues for threshold response.

Kogevinas et al., 1994

- Kogevinas Conclusion - study inadequate to rule out cancer from styrene
- Profile Conclusion - study provides limited evidence of cancer

Delzell et al., 2006

- When potential confounders are included, no styrene related increases.
- Profile asserts DMDTC is not a confounder because it has not been demonstrated to be a carcinogen.

Delzell et al., 2006

- Delzell Conclusion - no convincing evidence of styrene effect.
- Profile Conclusion - Increased risk of NHL and NHL-CLL combined.

No consistent effect asserted

- Kolstad et al., 2004 - increased Leukemia among workers with <1 year exposure.
- Kogevinas et al., 1994 - increased trend for total LH cancers
- Delzell et al., 2006 - increased NHL

Conclusion of human studies

- No consistent effect asserted
- Conclusions about Kogevinas and Delzell contrary to authors conclusions
- Criteria - “causal association is credible” is not met

Animal Studies

- NTP criteria for sufficient evidence
- A. increased tumors in multiple species - not true for styrene
- B. increased tumors in multiple organs - not true for styrene
- C. increased tumors by multiple routes of exposure - asserted in Draft Profile
- D. less than sufficient, but belongs to well-known class - asserted in Draft Profile

C. Two routes of exposure

- Clear evidence by inhalation
- Profile asserts clear evidence by oral compared to new historical control, using studies from different lab.
- Original publication by NCI debated between suggestive and no evidence, concluded suggestive
- 4 oral studies - no more than suggestive evidence

C. Two routes of exposure

- IARC Conclusion - Animal Data provide limited evidence, not sufficient evidence.
- Clear evidence by inhalation; suggestive evidence by oral
- Criteria for clear evidence by two routes not met

D. Belongs to well-known class

- Profile asserts -metabolized to epoxide; epoxides are reasonably anticipated or known to be carcinogens.
- Evidence does not support a role of SO in styrene-related mouse lung tumors

D. Belongs to well-known class

- Mode of Action Data- demonstrate styrene belongs to a class of chemicals that are metabolized in mouse lung by CYP2F2 to cytotoxic metabolites. Rats produce less of these metabolites and do not develop cytotoxicity or lung tumors. Humans produce even less.

Conclusion

- Styrene data do not meet NTP criteria for reasonably anticipated
 - Causal association of cancer to styrene in humans not credible
 - Clear evidence of increased tumors in animals in only 1 specie, 1 organ, and by 1 route of exposure
 - Mode of action data indicate mouse lung tumors not relevant to human risk

Conclusion

I urge you to tell the NTP staff that the scientific information cited in the draft substance profile for styrene :

1. is NOT technically correct,
2. is NOT clearly stated, and
3. does NOT support the NTP 's policy decision regarding its listing in the RoC.